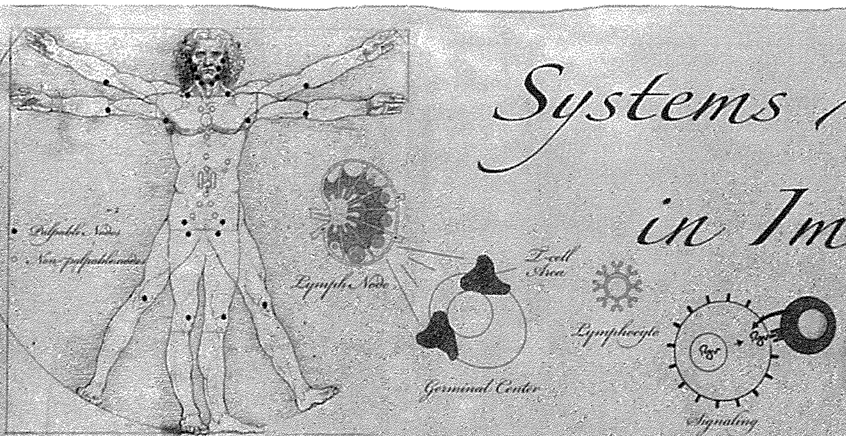

Systems Approaches in Immunology:

Advances and challenges in multi-scale modeling

January 10-11, 2010
Santa Fe, New Mexico, USA

Conference Proceedings

International Workshop on

Systems Approaches in Immunology:

Advances and challenges in multi-scale modeling

January 10-11, 2010
La Fonda Hotel, Santa Fe, New Mexico, USA

Agenda

Sunday, January 10th

9:30-12:00 *Systems approaches in innate and humoral immunity*
12:00-12:45 General Discussion
14:30-16:35 Contributed Talks - Systems approaches in immunity
16:35-18:00 Poster Session
18:00 – 19:00 Plenary Lecture

Monday, January 11th

9:00-12:00 Systems approaches in cellular immunity
12:00-12:45 General Discussion
14:30-18:15 Contributed Talks - Systems approaches in cellular immunity

Scientific Organizers:

Vitaly V. Ganusov
Steven H. Kleinstein
Ruy M. Ribeiro
Alan S. Perelson

Sponsors:

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Sunday, January 10th

***Session 1* - Systems approaches in innate and humoral immunity**

Chairs: Steven Kleinstein, Stephanie Forrest

9:30-9:40 Introduction

9:40-10:10 Bridget Wilson (UNM): High Resolution Technologies Capture FceRI Organization and Receptor Dynamics: the Need for Spatial Stochastic Simulation Approaches

10:10-10:40 Aaron Dinner (U Chicago): Genetic circuit architectures underlying choice of effector B cell fates

10:40-11:10 Phil Hodgkin (WEHI, AU): B-cell differentiation: order from manipulating randomness

11:10-11:30 Coffee Break (Santa Fe Room)

11:30-12:00 Martin Meier-Schellersheim (NIH): Automated quantitative analysis and computational reconstruction of 3D fluorescence microscopy data – application to lymphocyte data

12:00-12:45 General Discussion

12:45-14:30 Lunch (On your own)

Session 2 *-* ***Contributed Talks on Systems approaches in immunity***

Chairs: Vitaly Ganusov and Ruy Ribeiro

14:30-14:55 Anu Chaudhary (LANL): Studying protein-protein interactions underlying the innate immune response

14:55-15:20 Raibatak Das (UBC): Extraction of membrane-receptor binding kinetics from single-particle tracking data

15:20-15:45 Bin Hu (UNM): A model of early events in T-cell receptor signaling

15:45-16:10 Ramit Mehr (Bar-Ilan University): B Cell mutation and selection in autoimmune disease as inferred from mutation analyses of immunoglobulin variable region genes

16:10-16:35 German Nudelman (Mount Sinai, NY): Agent-based tripwire model explains paradoxical response to virus infection in human dendritic cells

16:35-18:00 Poster Session and Reception (Santa Fe Room)

Plenary Session

Chairs: Miles Davenport and Phil Hodgkin

18:00-19:00 *Bali Pulendran (Emory): Systems approaches to dissect immunity following vaccination with the yellow fever vaccine.*

High Resolution Technologies Capture FceRI Organization and Receptor Dynamics: The Need for Spatial Stochastic Simulation Approaches

Bridget S Wilson, Nicholas Andrews, Patrick Cutler, Keith Lidke, Janet M. Oliver, Amanda Carroll-Portillo, Jeremy Edwards and Diane Lidke, Jerilyn Timlin[2]

Department of Pathology, University of New Mexico, Albuquerque, NM; [2]Sandia National Laboratories, NM

We have applied a combination of high resolution microscopy approaches to study the membrane organization of FceRI, its signaling partners and the local lipid environment. Total internal reflection fluorescence imaging (TIRF), single particle tracking and electron microscopy methods are used to visualize receptor reorganization and dynamics at nanoscale spatial and temporal resolutions. These studies make use of novel probes, including ligand-nanogold, IgE-conjugated quantum dots and FITC-cholesterol derivatives. Recent work using both soluble ligands of defined valency, as well as presentation of monovalent ligands on supported lipid bilayers, provide new insights into the role of receptor density and crosslinking in triggering mast cell signaling. Novel observations include the first live cell imaging of membrane proteins transiently trapped in actin corrals and the first descriptions of the mast cell "synapse." These studies form the basis of new spatial stochastic simulation approaches to explore the relationships between membrane architecture, local receptor densities and diffusion-limited processes to control signal transduction.

Genetic circuit architectures underlying choice of effector B cell fates

Aaron R. Dinner

Department of Chemistry and Institute for Biophysical Dynamics, University of Chicago, Chicago, IL 60637, USA

Understanding how proteins contribute to biological regulation can require elucidating the collective dynamics of a network of molecular interactions. With Harinder Singh and his group, we have assembled minimal gene regulatory networks that govern cell-fate choice for formation and function of the immune system. In this talk, I will focus on a network in B lymphocytes that processes antigen receptor signal strength; quantitative modeling reveals how this network leads to an unusual developmental trajectory that transiently passes through a germinal center state which promotes receptor affinity maturation and immunoglobulin class switching before terminally differentiating into antibody secreting plasma cells. Beyond enabling the competing demands for somatic hypermutation, class switch recombination, and antibody secretion to be balanced during humoral immune responses, the gene regulatory architecture studied here provides a general mechanism for quantitative variations in a signal to be translated to a binary choice involving tunable duration of an expression program.

B-CELL DIFFERENTIATION: ORDER FROM MANIPULATING RANDOMNESS

P. D. Hodgkin[1], M.R. Dowling[1], J.F. Markham[2], K.R. Duffy[3], M.L.Turner[1], C.J. Wellard[1]
[1]Division of Immunology, The Walter and Eliza Hall Institute of Medical Research, Parkville, VIC, [2] National Information and Communications Technology Australia, Parkville, VIC, Australia, [3]Hamilton Institute, National University of Ireland, Maynooth, Ireland.

Careful quantitative experiments following B cell populations or tracking individual cell fates reveal relatively simple cellular rules operating independently within each cell. These experiments also reveal an extraordinary degree of autonomy, and variability in the behaviour of individuals despite a high degree of predictability and certainty in the population system outcomes. These data suggest an hypothesis where the seemingly ubiquitous variation is itself a design feature and should not be ignored. To test this hypothesis we developed quantitative mathematical models of the adaptive immune response built on modular units in all cells controlling times to die, to divide and to differentiate and that incorporate the stochastic features measured in our experiments. These models reliably recreate the complex B cell response and can explain much of the incredible heterogeneity and diversity that emerges over time after B cell stimulation. Together our models suggest a simplified theory of immunity and its evolution where control over stochastic generation of variable outcomes is the fundamental design paradigm. This theory also suggests a logical solution to the multi-scale problem – how to accommodate and structure information into useful models that operate at different organizational levels.

Automated quantitative analysis and computational reconstruction of 3D fluorescence microscopy data – application to lymphocyte data

Frederick Klauschen, Martin Meier-Schellersheim
Program in Systems Immunology and Infectious Disease Modeling, Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, MD

Numerical analyses and computational models of (multi-)cellular processes are increasingly based on fluorescence microscopy data with high spatial and temporal resolution. Extracting the relevant quantitative features and spatial structures from those images and transforming them into computationally accessible formats is typically one of the most time-consuming and error-prone steps during such analyses. We developed a set of tools that permit fully automated analyses of morphological features and cellular interaction behavior in 3D fluorescence microscopy images. We will demonstrate the application of our approach to images showing the spatial association of dendritic cells with the fibroblastic reticular cell network within lymph nodes and to microscopy data regarding T-B lymphocyte synapse formation. Moreover, we will show how 3-D confocal images of single cells can be used to generate numerical representations of cellular membranes that may serve as the basis for realistic, spatially resolved computational models of membrane processes or intracellular signaling.

This work was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Allergy and Infectious Disease

Studying Protein-Protein Interactions Underlying the Innate Immune Response

Anu Chaudhary[1], Kumkum Ganguly[1], Kamalika Nag[1], Stephanie Cabantous[1], Geoffrey S. Waldo[1], William S. Hlavacek[2] and Chang-Shung Tung[2]
Biosciences Division[1], Theoretical Division[2], Los Alamos National Laboratory, Los Alamos, NM

Toll-like receptors (TLRs) offer the first line of host defense by recognizing the danger signals of pathogen and by inducing intracellular signaling that culminate in appropriate innate immune responses to counter the invading pathogens. Subsequent to signal recognition, interaction between death domain (DD) and toll-interleukin receptor homology domain (TIR) initiate intracellular signaling in the host. Many pathogens such as uropathogenic *E. coli* and *B. melitensis* have evolved mechanisms to evade this host machinery for detecting danger signal by TLR. One such mechanism involves secreting TIR-like proteins that abrogate the host innate immune response.

We have developed cell-based assays to investigate the nature and specificity of interactions involving TIR and DD, and the ability of pathogen TIR-like proteins to disrupt them. Studies involve developing the split-luciferase assay to study these interactions. Using the split-green fluorescence protein (GFP) technology, developed in the Waldo laboratory, we have examined folding and aggregations of these domains. Additionally, we are using triple-split GFP technology to investigate specificities of interactions of these protein-protein interactions.

We have investigated dimerization of adaptor protein MyD88, a critical component of the host innate immune response. MyD88 contains two domains, a DD and a TIR domain. The role of these domains in dimerization remains unclear. Preliminary data from these studies indicates that DD of adaptor protein MyD88 mediates strong interactions with its own DD. Additionally, MyD88-DD interactions are observed with MyD88- TIR domain and with full-length MyD88. Structural modeling approaches have allowed us to develop a model of MyD88 dimerization, and identify critical ion pairs that play a role this dimerization. Ongoing studies are exploring the ability of *Brucella* TIR-like proteins to disrupt MyD88 and other adaptor protein interactions.

Extraction of membrane-receptor binding kinetics from single particle tracking data

Raibatak Das
University of British Columbia, Canada

Nearly all immune responses are mediated by cell-surface receptors when they encounter a cognate antigen, often present at the surface of another cell. Activated receptors further interact with downstream signaling proteins, that may either be present on the membrane or recruited from the cytosol. It is challenging to accurately quantify the kinetic parameters of these 2D interactions under physiological conditions using traditional biochemical assays or biaCORE experiments where one or both binding partners are in solution (i.e. 3D). We have developed a novel analysis of single particle tracking (SPT) data that reveals in-situ binding kinetics for the interaction between a cell-surface receptor and a homogeneously distributed binding partner. We show that, with certain simplifying assumptions, particle trajectories can be regarded as the outcome of a two-state hidden Markov model. Using simulated trajectories, we demonstrate that this model can be used to identify key biophysical parameters for such a system, namely the diffusion coefficients of the underlying states, and the rates of transition between them. We use a stochastic optimization scheme to compute maximum likelihood estimates of these parameters. We have applied this analysis to single-particle trajectories of the integrin receptor LFA-1 and the receptor protein tyrosine phosphatase CD45 on live T cells. Our analysis reveals that the dynamics of both these proteins are well-captured by a two-state diffusion model with large-scale changes in their interaction with the actin cytoskeleton upon cellular activation.

A Model for Early Events in T-cell Receptor Signaling

Bin Hu[1, 2, 3], **Ryan N. Gutenkunst**[3, 4], **Lily Chylek**[1], **William S. Hlavacek**[1, 2, 3,4]
[1]*Department of Biology, University of New Mexico, NM;* [2]*Center for the Spatiotemporal Modeling of Cell Signaling, University of New Mexico Cancer Center, NM;* [3]*Theoretical Biology and Biophysics Group, Theoretical Division, Los Alamos National Laboratory, NM;* [4]*Center for Nonlinear Studies, Los Alamos National Laboratory, NM*

During T lymphocyte activation, many proteins are phosphorylated and dephosphorylated on tyrosine residues. Through these modifications, proteins gain or lose the ability to bind other proteins containing SH2 domains or gain or lose the ability to catalyze reactions. To better understand the dynamics of tyrosine phosphorylation, we have developed a rule-based model of early events in T-cell receptor signaling in Jurkat T cells. Proteins and protein interactions were included in the model based on published literature and temporal phosphoproteomic data. Our model accounts for 20 proteins and 22 tyrosine phosphorylation sites. Time courses of tyrosine phosphorylation predicted by the model are consistent with measured time courses. This model represents an effort to link quantitative proteomics data to detailed computational modeling. The model constitutes a detailed hypothesis about the mechanism of T-cell activation triggered by cross-linking of TCR/CD3 and CD28.

B cell Mutation and Selection in Autoimmune Diseases as Inferred from Mutation Analyses of Immunoglobulin Variable Region Genes

Neta S. Zuckerman[a], **Wendy A. Howard**[b], **Jacky Bismuth**[c], **Kate Gibson**[b], **Hanna Edelman**[a], **Helena Hazanov**[a], **Michal Barak**[a], **Hanna Edelman**[a], **Shira Hess**[a], **Hadas Shcolnik**[a], **Sonia Berrih-Aknin**[c], **Deborah Dunn-Walters**[b], and **Ramit Mehr**[a,*].
[a] *The Mina and Everard Goodman Faculty of Life Sciences, Bar-Ilan University, Israel;* [b] *King's College London Medical School, UK;* [c]*CNRS UMR 8162, Hôpital Marie Lannelongue, Université Paris-Sud, France*

B cells have been found to play a critical role in the pathogenesis of several autoimmune (AI) diseases. A common feature amongst many AI diseases is the formation of ectopic germinal centers (GC) within the afflicted tissue or organ, in which activated B cells undergo expansion, somatic hypermutation (SHM) and antigen (Ag)-driven selection on their immunoglobulin variable region (IgV) genes. However, it is not yet clear whether these processes occurring in ectopic GCs are identical to those in normal GCs. The analysis of IgV mutations has aided in revealing many aspects concerning B cell expansion, mutation and selection in GC reactions. We have applied several mutation analyses, based on lineage tree construction, to a large set of data, containing IgV productive and non-productive heavy and light chain sequences from several different tissues, to examine three of the most profoundly studied AI diseases – Myasthenia Gravis (MG), Rheumatoid Arthritis (RA), Multiple Sclerosis (MS) and Sjögren's Syndrome (SS). We have found that MG, RA and MS sequences exhibited normal mutation spectra and targeting motifs. However, the results imply a stricter selection compared to normal controls, and this was more apparent in RA. SS sequence analysis results deviated from normal controls in both mutation spectra and indications of selection, also showing differences between light and heavy chain IgV and between different tissues. Overall, our results revealed several differences between the mutation patterns in the AI diseases examined, and those in normal controls. These differences probably result from the differences between the microenvironmental influences to which ectopic GCs are exposed to, and those in normal secondary lymphoid tissues.

Agent-based tripwire model explains paradoxical response to virus infection in Human Dendritic Cells

German Nudelman[1], **Yishai Shimoni**[1], **Jianzhong Hu**[2], **Fernand Hayot**[1], **James G. Wetmur**[2], **Stuart C. Sealfon**[1]

[1]*Center for Translational Systems Biology and Department of Neurology, Mount Sinai School of Medicine, NY;*
[2]*Department of Microbiology, Mount Sinai School of Medicine, NY*

Viral infection leads to the production of type I interferons, which act through the interferon receptor to activate transcription of many genes, including DDX58, which encodes viral detector protein - Rig-I. However, examination of the kinetics of transcription of DDX58 and interferon beta (IFNB1) following viral infection shows that induction of DDX58 occurs earlier, not as naively expected later, than the induction of IFNB1. One possible explanation for this paradox is that the measured average responses do not reflect the variations in individual cell responses. A few "tripwire" cells could induce IFNB1 early and secrete biochemically undetectable levels of IFN that are still able to induce DDX58 in other cells.
To test this hypothesis we have developed a space and time multiscale agent based model of the Human Dendritic Cells (DCs) viral infection process.

The Monte Carlo method is employed to explicitly simulate the spatial layer using biophysically measured parameters. It contains DCs expressing TypeI IFN receptors on the cell surface, surrounded by IFN molecules diffusing within a medium. On the intracellular scale, the dynamics of IFNB1 and DDX58 transcript and protein dynamics is modeled using a Gillespie algorithm. The scales are combined by introducing a modification into the Gillespie algorithm that allows its synchronization with the Monte Carlo time steps. The simulation Graphic User Interface visualizes the simulation in real time by generating an animation, depicting the state of the cell surface at each iteration.

Single cell experiments performed on human DCs infected by Newcastle Disease Virus (NDV) were consistent with the simulation results, supporting the hypothesis that IFNB1 transcription in early responding cells is sufficient for significant DDX58 induction in the population

Monday, January 11th

Session 3 - Systems approaches in cellular immunity

Chairs: Rob De Boer and Alan Perelson

9:00-9:30 Dan Coombs (UBC): A TCR/pMHC confinement-time model of T-cell activation

9:30-10:00 Rustom Antia (Emory): Modeling the dynamics persistent infections

10:00-10:30 Miles Davenport (UNSW, AU): Decision making during T cell responses

10:30-11:00 Coffee Break (Santa Fe Room)

11:00-11:30 Thorsten Mempel (Harvard): T cell migratory dynamics during an anti-tumor immune response

11:30-12:00 Jurgen Westermann (Luebeck, GE): Principles of T-cell migration: Facts and fiction

12:00-12:45 General Discussion

12:45-14:30 Lunch (On your own)

Session 4 - **_Contributed talks on Systems approaches in cellular immunity_**

Chairs: Rustom Antia and Bridget Wilson

14:30-14:55 Becca Asquith (Imperial College): What determines the outcome of HTLV-1 infection?

14:55-15:20 Fred Adler (Utah): No one remembers when the second team wins: strategies of rhinovirus immune manipulation

15:20-15:45 Stanca M Ciupe (Duke): Models of antibody responses during HIV infection

15:45-16:10 Paul Thomas (St. Jude's): Memory potential is determined by priming epitope number

16:10-16:30 Coffee Break (Santa Fe Room)

16:30-16:55 Jose Borghans (Utrecht): Naive T-cell dynamics in mice and men: Recent thymic emigrants revisited

16:55-17:20 Iren Bains (University College London): Heterogeneity within thymic emigrants: a mechanistic explanation for T cell homeostasis?

17:20-17:45 Irina Grigorova (UCSF): T-cell recirculation through mouse lymph nodes: insights from 2-photon imaging, quantitative analysis and modeling of T-cell egress

17:45-18:10 Rob De Boer (Utrecht): Analyzing immune cell migration

18:10-18:15 Adjournment and final thoughts – Organizing Committee

A TCR/pMHC confinement-time model of T cell activation

Daniel Coombs
University of British Columbia, Canada

T cell activation is a crucial step in the adaptive immune response. T cells can be activated by signals due to bonds between their T cell receptors (TCR) and peptide-major-histocompatibility-complex (pMHC) presented on antigen-presenting-cells. But so far as we can tell, the chemical bonds that form between TCR and pMHC are weak and transient. As part of a quantitative theory of immune activation, it would be useful to understand how the kinetics of these chemical bonds control the T cell response. I will describe recent work on a model of receptor binding, unbinding, and re-binding. This model performs well in relation to experimental data and has interesting theoretical properties. This is joint work with Omer Dushek, Milos Aleksic, and Anton van der Merwe, among others.

Modeling the dynamics of acute and persistent infection

Rustom Antia
Emory University, GA

I will begin by outlining simple ecologically motivated models for the dynamics of immune responses. The first half of the talk will consider the use of these models to understand the dynamics of CD8 T cell responses during acute infections and the generation of immunological memory. The second half of the talk will consider preliminary work on modeling persistent infections. I will first outline a model for the dynamics of virus and immune cells during infections of mice the Clone13 strain of LCMV that causes a chronic infection. The model will be used to understand the course of pathology following chronic LCMV infections. Finally I will extend our model to consider antigenically varying pathogens (such as malaria) with startling results that run counter to conventional wisdom concerning the importance of cross-reactive immune responses.

Decision making during T cell responses.

Miles Davenport
University of New South Wales, Australia

Following acute infection CD8+ T cells undergo rapid division and differentiation to form a large population of 'effector' cells capable of fighting infection. This is followed by major contraction where 5% of cells survive to form a pool of long-lived 'memory' cells. How cells 'decide' whether to become effector or memory cells is a major question, and a variety of lineage relationships have been proposed to explain this.

The expression of the adhesion molecule CD62L is one marker that has been used to identify different stages of T cell differentiation, being high on naïve cells, low on 90% of cells during the effector phase, followed by a gradual conversion back to a predominantly CD62L^{high} phenotype during memory. We have investigated changes in the expression of CD62L expression during an immune response using two separate experimental models. Firstly, we studied an adoptive transfer system where graded numbers (3200 – 400 000) of antigen-specific (OT-1) CD8+ T cells are transferred into an animal, followed by infection with *Listeria monocytogenes* bearing the OVA epitope. We observed that OT-1 expansion is reduced in higher adoptive transfer frequencies and that these populations also have a higher proportion of cells remaining CD62L^{high}. These results suggest that loss of CD62L expression may be intrinsically linked to the number of divisions cells have undergone *in vivo*. We investigated this by studying how a division-linked differentiation mechanism, where a proportion of cells CD62L^{high} become CD62L^{low} with each division, can account for experimental data. We find that a simple process where 20% of CD62L^{high} cells convert to CD62L^{low} phenotype at each division can accurately predict differences in CD62L expression between adoptive transfer populations and between different days post infection within individual mice.

In a separate set of experiments, we studied cell phenotype in the endogenous (non-transgenic) response to influenza infection in mice by looking at the T cell receptor repertoire in cells expressing different levels of CD62L. We found that the CD62Llow repertoire showed strong clonal dominance by a few TCR, which were also found in the CD62L high compartment. By contrast, the repertoire in the CD62Lhigh compartment was much more diverse, and contained many clonotypes not present in the CD62Llo subset. Our modeling suggests that this distribution of clonotypes is consistent with a process of division-linked differentiation driving the loss of CD62L expression during acute infection in vivo.

T cell migratory dynamics during an anti-tumor immune response

Thorsten R. Mempel
Massachusetts General Hospital and Harvard Medical School, USA

Recent technological advances in photonics are making intravital microscopy an increasingly powerful approach for the mechanistic exploration of biological processes in the physiological context of complex native tissue environments. Direct, dynamic and multiparametric visualization of immune cell behavior in living animals at cellular and subcellular resolution has already proved its utility in auditing basic immunological concepts established through conventional approaches and has also generated new hypotheses that can conversely be complemented and refined by traditional experimental methods.

We are developing multiphoton intravital microscopy methods to investigate the role of cytotoxic T lymphocytes in the immune response against cancer and to mechanistically explore the network of cellular interactions that together result in either immunity or tolerance against malignant growths. Current progress from our work will be presented.

Principles of T-cell migration: Facts and fiction

Juergen Westermann
University of Luebeck, Germany

T cells are involved in the pathogenesis of many diseases. To exert a pathological effect, T cells enter the tissues. We show that the determination of their entry site requires isolation of the respective T cell population, injection into genetically un-manipulated animals, and identification of the cells in vivo at various time points after injection. We indicate variables influencing in vivo migration experiments artificially, and outline how resulting problems can be avoided. Reviewing experiments performed according to the outlined criteria reveals two types of migration patterns for T cell subsets in vivo: 1) Naive and memory T cells enter lymphoid and non-lymphoid organs in comparable numbers, but selectively accumulate in lymphoid tissues over time. 2) Activated T cells, too, enter lymphoid and non-lymphoid organs in comparable numbers. However, most of them die within 24 hours. Such information is necessary for developing a systematic view of T-cell migration and for understanding its role in the pathogenesis of T cell mediated diseases.

What determines the outcome of HTLV-1 infection?

Aidan MacNamara, Aileen Rowan, Ulrich Kadolsky, Graham Taylor, Charles Bangham, Becca Asquith
Dept Immunology, Imperial College London, UK

Human T lymphotropic virus-I (HTLV-I) is a persistent retrovirus. HTLV-I-infected individuals show considerable heterogeneity in their set point proviral load and clinical outcome. There is evidence that HTLV-I-specific CD8+ T cells lower proviral load and reduce the risk of the associated inflammatory disease HAM/TSP. However, what constitutes a protective CD8+ T cell response is poorly understood.

Results.
• Class I alleles previously associated with reduced proviral load and HAM/TSP prevalence were predicted to bind epitopes from the viral protein HBZ significantly more strongly than an allele associated with increased proviral load and HAM/TSP prevalence.
• Asymptomatic carriers had an HLA class I genotype that predisposed them to bind epitopes from HBZ significantly more strongly than HAM/TSP patients.
• Individuals whose HLA class I genotype predisposed them to bind HBZ epitopes had a significantly reduced proviral load.
• Across all HTLV-I proteins, those proteins that were preferentially targeted by asymptomatic carriers were those associated with a greater reduction in proviral load.

In conclusion, we demonstrated that protection is not limited to a small subset of HLA class I alleles previously associated with disease status and proviral load, but is more generally associated with HLA class I alleles that bind strongly to HBZ. Furthermore, across all alleles and all proteins, the protection from HAM/TSP conferred by HLA binding was significantly associated with the reduction in proviral load associated with HLA binding. This strongly suggests that CD8+ T cells play a significant role in the control of HTLV-I infection with CD8+ cells specific for HBZ, not the immunodominant protein Tax, being the most effective at reducing proviral load and risk of HAM/TSP.

No one remembers when the second team wins: Strategies of rhinovirus immune manipulation

Fred Adler
University of Utah, UT

Rhinoviruses, consisting of about one hundred serotypes that cause most common colds, are completely cleared by the host immune system after causing minimal cell death and often without inducing long-term immune memory. This small mystery within hosts has tremendous implications for the population dynamics, diversity, and evolution of these viruses. In addition to infecting and killing host epithelial cells, the majority of rhinoviruses also bind to receptors on antigen-presenting cells (APCs), altering their behavior without actually infecting them. Virally bound APCs exit peripheral tissue more slowly, and the IL-12 they release to initiate the appropriate Th1 response in the lymph node instead acts near the site of infection to activate natural killer (NK) cells that produce IFN-gamma and help in viral clearance. Those APCs that reach the lymph node arrive later and in a more tolerogenic state, further inhibiting the Th1 response and memory. Rhinoviruses thus use a multi-level strategy to redirect a systemic adaptive immune response into a spatially-localized innate response. Understanding how this strategy has evolved and been so successful requires comparing the competitive interactions between subtle viral variants both within hosts and in the whole population.

Models of antibody responses during HIV infection

Stanca M Ciupe[1], Thomas B Kepler
1. University of Louisiana, Lafayette, LA

During the course of an individual's infection with Human Immunodeficiency Virus, the virus population consists of a distribution of different variants, produced by mutation and selection. Biological experiments have shown that neutralizing antibodies fail to offer long-term protection because they are primarily strain-specific and lag behind viral evolution. While monoclonal neutralizing antibodies of broad reactivity against diverse HIV strains have been identified in vitro, they are rarely detected in vivo. In this study, we design mathematical models that propose mechanisms related to antibody failure, focusing on the roles of competition and cross-reactivity among antibodies as well as viral evolution. We hypothesize that broadly neutralizing antibodies develop alongside strain-specific neutralizing antibodies, and investigate whether their small level (perhaps undetectable *in vivo*) is due to competition with the fit, strain-specific antibody.

Memory potential is determined by priming epitope number

Paul Thomas
St. Jude Children's Hospital, TN

Immunization with an engineered H1N1 influenza A virus disrupted for two dominant $CD8^+$ T cell epitopes led to substantially increased subdominant responses following respiratory infection with the comparable knockout or wildtype H3N2 virus. However, challenge with the knockout virus after wildtype priming did not result in enhanced secondary responses. The basis of this compensatory effect is thus established at the time of priming, though there were no obvious differences in memory T cell numbers prior to secondary virus challenge. The enhanced recall responses to subdominant epitopes were, however, modified in both breadth and character. Single cell analysis of "subdominant" TCR CDR3b regions showed greater evidence of sharing indicative of broader memory repertoire recruitment between knockout-primed mice, in contrast to the more "private" response characteristic of the wildtype infection. The expanded subdominant $CD8^+$ T cell populations in the knockout-primed mice also had a lower overall TCR avidity. Mathematical models of immunodominance that capture features of this behavior have been generated. Thus, priming in the context of fewer epitopes recruits a broad repertoire with increased memory potential, suggesting possibilities for vaccination protocols skewed towards minor epitopes that might, for example, be less susceptible to immune escape. The utility of these models for understanding the molecular mechanisms of memory will be discussed.

Naive T-cell dynamics in mice and men: Recent thymic emigrants revisited

Tendai Mugwagwa, Ineke den Braber, Liset Westera, Elise H.R. Schrijver, Gerrit Spierenburg, Koos Gaiser, An F.C. Ruiter, Mariette T. Ackermans, Frank Miedema, Kiki Tesselaar, Rob J. de Boer, José A.M. Borghans

UMCU, Netherlands

The contribution of thymus output to the maintenance of the naive T-cell pool is still controversial. Using a combination of deuterium labeling, thymectomy experiments and mathematical modeling, we show that, throughout life, naive T-cell maintenance in mice depends almost completely on thymus output. In contrast to the situation in men, we found that peripheral naive T-cell division hardly contributes to the naive T-cell pool in mice. These findings were confirmed by the absence of T-cell receptor excision circle (TRECs) dilution of mouse naive T cells with age. Mathematical analysis of the experimental data shows that naive $CD4^+$ and $CD8^+$ T cells in young adult mice have a life expectancy of about 7 and 11 weeks, respectively.
Both deuterium labeling in young and old mice, and thymectomy experiments provided no evidence for separate dynamics of recent thymic emigrants (RTE) and resident naive T cells in mice. We show that even the thymus-grafting experiments by Berzins and colleagues, which formed the basis for the concept that RTE form a dynamically distinct sub-population in the naive T-cell pool, are compatible with a kinetically homogeneous T-cell population. Also in humans, we found no evidence for a kinetically distinct RTE population, using deuterium labeling.
In conclusion, both in humans and in mice there is no evidence that RTE form a kinetically distinct sub-population of the naive T-cell pool. There is, however, a qualitative difference between naive T-cell dynamics in mice and men, because the vast majority of naive T cells in mice are produced by the thymus, while in humans they are produced by peripheral proliferation. These differences in naive T-cell dynamics between mice and men point to a serious limitation regarding extrapolation from mouse to man and *vice versa*.

Heterogeneity within thymic emigrants: a mechanistic explanation for T cell homeostasis?

Iren Bains[1,2], Andrew Yates[3], Robin Callard[1,2]

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We explore the way in which T cells recently emigrated from the thymus are incorporated into the circulating naive T cell pool in order to better understand how T cell receptor diversity and T cell numbers are maintained in the face of diminishing thymic export with age and after thymectomy. The path taken by a thymic emigrant when it enters the peripheral T cell pool is difficult to follow experimentally. CD31 and Protein tyrosine kinase 7 (PTK7) have been used as surrogate markers of recent thymic emigration[1] and circulating PTK7+ naïve-CD4+ T cells are thought to be immediate peripheral descendants of single-positive thymocytes and precursors of more mature PTK7-naiveCD4+ T cells.

Here, we propose that there is inter-cellular variation in the time taken to differentiate from PTK7+ to PTK7- naïve CD4+ T cells. Inter-cellular heterogeneity provides a mechanistic explanation for the less dynamic T cell phenotype observed in elderly individuals as well as the reduced turnover of PTK7+ T cells following thymectomy. A mathematical model was used to estimate the distribution of residency times of cells within the peripheral PTK7+ population by fitting to published experimental data from thymectomised patients and the half-life of PTK7 expression on T cells leaving the thymus was estimated. The model was validated by using the estimated distribution of residency times in combination with a quantitative estimate for daily thymic export[2] to predict the accumulation of cells with age. This was consistent with observed changes in circulating PTK7+ naïve-CD4+ T cell numbers.

The changing composition of the peripheral PTK7+NaïveCD4+ T cell population was also examined. The estimated distribution suggests that there is a small tail-end of long-lived PTK7+ cells within each cohort of thymic emigrants that will accumulate with age. As a result, the average post-thymic age of cells is predicted to increase linearly with the age of the host suggesting that stochastic variation within each cohort of T cells leaving the thymus can have a dramatic effect on the peripheral population over time. PTK7+ cells do not therefore necessarily represent a population of recent thymic emigrants. Furthermore, the model was used to explore the impact of thymectomy on the size and post-thymic age of the PTK7+ naïve-CD4+ T cell population in individuals of different ages. The model predicts an accelerated increase in the average post-thymic age of residual PTK7+ naïve-CD4+ T cells following thymectomy.

1. Haines et al. *J Exp Med* 206: 275-285
2. Bains et al. *J Immunol* 183: 4329-36

T cell recirculation through mouse lymph nodes: insights from 2-photon imaging, quantitative analysis and modeling of T cell egress.

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Lymphocyte recirculation between blood, lymphoid organs and lymph is crucial for antigen scanning and effector functions of lymphocytes. Although a lot was already known about lymphocyte entry into the lymph nodes (LNs) from the blood, the anatomical location and mechanism of lymphocyte exit from the LNs was unclear. By 2-photon intravital imaging we identified cortical LYVE-1^+ sinuses as the sites of lymphocyte exit and suggested a multistep model of T cell exit from the LNs. Previous work indicated that intrinsic expression of $S1P_1$ receptor by T cells and a gradient of its ligand, S1P, are required for T cell egress. Quantitative characterization of T cell migration in relation to the cortical sinuses demonstrated that T cells migrate to the sinuses and probe their surface in an $S1P_1$-independent manner; however, commitment to transmigration into the sinus requires expression of $S1P_1$ on T cells. After transmigration into cortical sinuses T cells are retained and passively carried by flow towards "portals" in the subcapsular space proximal to the medullary region and efferent lymphatics. Based on the quantitative 2-photon imaging data and confocal 3D reconstruction of High Endothelial Venules (HEVs) and LYVE-1^+ sinuses we built a quantitative model of T cell migration and exit from the LNs. The model suggests that T cells go through a few rounds of entry into the LYVE-1^+ sinuses before they can reach the efferent lymphatics and egress from the LNs.

Analysing immune cell migration

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The visualization of the dynamic behaviour of and interactions between immune cells using time-lapse video microscopy has an important role in modern immunology. To draw robust conclusions, quantification of such cell migration is required. This is far from trivial because imaging experiments are associated with various artifacts that can affect the estimated positions of the immune cells under analysis, which form the basis of any subsequent analysis. We construct spatially explicit models of T cell and DC migration in LNs and show that several dynamical properties of T cells are a consequence of the densely packed LN environment. Our three-dimensional simulations suggest that the initial decrease in T-cell motility after antigen appearance is due to "stop signals" transmitted by activated DCs to T cells. Because imaging is typically restricted to experiments lasting 1 h, and because T cell-DC conjugates frequently move into and out of the imaged volume, it is difficult to estimate the true duration of interactions from contact data. We propose a method to properly make such an estimate of the average of the contact durations. The method is validated by testing it to our spatially explicit computer simulations.

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18. Immune System Decision-Making by Detection of Pathogen Growth
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1. Mathematical Model of a Three-Stage Innate Immune Response to Pneumococcal Lung Infection

Amber Smith
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Pneumococcal pneumonia is a leading cause of death and major source of human morbidity. The initial immune response plays an integral role in determining if an invasive pneumococcal disease is established and whether a favorable outcome occurs. To investigate the coordination of immune responses and evaluate the relative contributions of individual components, we take a systematic approach by building a mathematical model from subsystems that describe the succession of resident alveolar macrophages, neutrophils and monocyte-derived macrophages into the lung. Our model confirms that for small initial numbers of pneumococci, rapid clearance from the airways is the result of an efficient alveolar macrophage response. However, as these cells become overwhelmed with higher initial values, they switch to orchestrating the recruitment of neutrophils by releasing proinflammatory cytokines. Neutrophils may be sufficient to clear intermediate initial values but have little effect on large pneumococcal densities. Finally, although macrophages are recruited following neutrophil decline, sustained bacteria growth is possible even with the presence of these cells. We hypothesize that damage caused by pneumococcal cytotoxicities plays a large role in the pathogenesis and may be a significant source of inflammation. Bacterial titer data from mice infected with S. pneumoniae are used to ensure our model behaves consistently with empirical observations.

2. Cooperation and competition determine CD8 T-cell immunodominance hierarchies

Andreas Handel
University of Georgia, GA

We (Andreas Handel and Rustom Antia) have previously used a simple mathematical model to study the immunodominance dynamics of the two most prominent CD8 T-cell populations during influenza infections in mice (Handel and Antia 2008, Journal of Virology). We were able to explain seemingly contradictory data from experimental studies.

For the current project, we (Andreas Handel and Paul Thomas) extend the previous study and consider data from additional epitope-specific CD8 T-cell populations. We find that while our previous model can explain some of the experimental observations, it fails to explain others. Specifically, the data show that in addition to the competition mechanism we discussed previously, there also seems to be "cooperation" between epitope-specific CD8 T-cells. By extending our model to include both competitive and cooperative mechanisms between the different T-cell populations we are able to fit the data.

3. Evolving and Quenching a Quorum in Digital Organisms

Benjamin E. Beckmann and Philip K. McKinley
Department of Computer Science and Engineering, Michigan State University, MI

Many bacteria rely on quorum sensing (QS) to coordinate the regulation of disease-causing genes. To determine cell density, they exchange molecular signals, called auto-inducers (AIs). By "counting" these signals, bacteria can detect density. Disrupting this communication effectively disables the ability to cooperatively inflict illness. Anti-infective therapies that disrupt, or quench, a quorum are currently under investigation as an alternative to traditional antibiotics for treating numerous diseases, including cystic fibrosis and methicillin-resistant Staphylococcus aureus. Whereas antibiotics aid in relieving illness by killing bacteria, thereby selecting for antibiotic resistance, QQ therapies attempt to "confuse" bacteria by affecting their communication. Therefore, QQ therapies should produce lower resistance. However, very little is known about the long-term effects of QQ therapies.

We apply digital evolution, a form of evolutionary computation, to better understand and help to predict the evolution of pathogenesis in bacteria. In digital evolution, a population of self-replicating computer programs exists in a computational environment and is subject to mutations and natural selection. Over generations, these "digital organisms" evolve to optimize resource usage and thrive when possible. Recently, we demonstrated that digital organisms can evolve to perform QS [1]. The evolutionary process produced individuals that coerce the behavior of their neighbors, much like auto-inducers coerce the behavior of bacteria. In [2], we extended this work by replicating, in silico, a laboratory experiment conducted with P. aeruginosa infections in mice [3]. We showed that the trends of the QQ therapies produced in digital organisms were consistent to those reported in [3]. In addition, we extended the experiment for many thousand generations beyond the introduction of the therapies. Projecting further into evolutionary time facilitates predictions of how systems may evolve in the presence of anti-infective therapies.

Our ongoing investigations focus on the evolution of signaling mechanism among QS bacteria, which is essential to our understanding of the potential effects of QQ therapies. Many bacteria have been shown to employ multiple QS systems, which are dependent on different signals. The application of a QQ therapy may produce an evolutionary pressure that has the potential to change how information is encoded within and, more interestingly, among channels. This type of adaptation could produce resistance, lessening the therapeutic benefits and potentially rendering them ineffective. Moreover, the speed at which adaptation occurs is of interest since it will directly affect the longevity of QQ therapies.

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[2] B. E. Beckmann, P. K. McKinley, and D. B. Knoester. Effects of communication impairments on quorum sensing. In Proceedings of the Third IEEE International Conference on Self-Adaptive and Self-Organizing Systems, pages 276Ð277, San Francisco, CA, USA, 2009.
[3] K. P. Rumbaugh, S. P. Diggle, C. M. Watters, A. Ross-Gillespie, A. S. Griffin, and S. A. West. Quorum sensing and the social evolution of bacterial virulence. Current Biology, 19(4):341Ð345, January 2009.

4. A comparative study of seasonal and non-seasonal dynamics of Buruli ulcer.

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Buruli Ulcer (BU) is a debilitating affliction that produces a very scaring ulcer. The disease, which is caused by Mycobacterium ulcerans has been postulated to be spread by a vector (waterbugs) whose breeding habits are determined by environmental factors and seasonal patterns. In this poster, we compare the seasonal dynamics of BU to its non-seasonal counterpart and show that seasonal dynamics typically affect the number of secondary cases of BU, which is the key to the spread of any disease.

5. MHC-I Molecules Exploit the Low G+C Content of Pathogenic Genomes for Increased Presentation

Jorg Calis, Gabino Sanchez-Perez & Can Kesmir
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Distinguishing self from non-self and pathogenic from non-pathogenic is a fundamental challenge to the immune system. Several pathogen associated molecular patterns (PAMPs) are used for this purpose by the innate immune systems. At the adaptive branch of immunity, however, the role of PAMPs is not well documented. Though the enhanced presentation of PAMPs by MHC molecules would facilitate self/non-self discrimination. By investigating the presentation of large sets of viruses and bacteria on most frequent human MHC (HLA) molecules, we analyze the presentation of pathogen-derived peptides by MHC molecules. The presentation rates of different organisms on different MHC molecules varies up to 6 fold. This variation can be explained by a strong (dis)preference for G+C content, which is reflected in amino acid frequencies. A low G+C content seems to be a universal signature for pathogenicity, i.e., a form of PAMP. Interestingly, a significant majority of HLA-A, but not HLA-B, molecules preferably present G+C low species. The analysis of HLA-A binding motifs excludes lack of diversity as an explanation for this collective HLA-A G+C negativity. Finally, we examine the G+C preferences of Chimpanzee and Rhesus Macaque MHC class I molecules and find the same preference for presenting G+C low organisms in both primates. Taken together, these results demonstrate that despite the fast evolution of MHC alleles, their extreme polymorphism, and large diversity in peptide-binding preferences, MHC molecules in different species can acquire a preference for presenting PAMPs.

6. Stochastic modelling of T cell repertoire diversity

Carmen Molina-Paris
University of Leeds, uk

T cells are specialised white blood cells that protect the body from infection and are also able to kill infected cells. T cells are characterised by the presence of a special receptor on their cell surface called T cell receptor (TCR). The specificity of the T cell, namely which pathogens it can recognise, is determined by the molecular structure of its TCR. T cells can be classified according to their TCRs. All T cells that have identical TCRs are said to belong to the same clonotype. There are two types of T cells: naive and memory. Naive T cells have not yet encountered pathogens and memory T cells have already encountered pathogen. In this talk, I will only consider the class of naive T cells. A diverse naive T cell pool is essential to protect against novel infections, as the immune system cannot predict which pathogens the organism will be exposed to during its life-time. A healthy adult human possesses approximately 10^(11) naive T cells, which belong to about 10^(7)-10^(8) different clonotypes. The reliability of the immune response to pathogenic challenge depends critically on the size (how many cells) and diversity (how many different TCRs or clonotypes) of the naive T cell pool of the individual. Experimental evidence suggests that interactions between TCRs with self-peptides (self-peptide = a fragment of a household protein) displayed on the surface of specialised cells, called antigen presenting cells (APCs), are important in controlling naive T cell numbers. Naive T cells undergo one round of cell division after receiving a survival stimulus from these specialized APCs. Whether or not a particular naive T cell can receive a survival signal from an specialized APC depends both on the TCR it expresses and the array of self-peptides displayed on the surface of the APC. Competition amongst naive T cells for these interactions regulates the diversity of the naive T cell pool.

We have made use of a probabilistic (stochastic) model to describe this competition. In particular, we have modeled the time evolution of the number of T cells belonging to a particular clonotype. Our results indicate that competition maximizes TCR diversity by promoting the survival of T cell clonotypes that are most different from each other in terms of the self-peptides they are able to recognise.

7. Modeling the Impact of Proliferation and Attrition on the Memory T-Cell Repertoire

Courtney Davis
University of Utah, UT

New infections change an individual's protective immunity to past diseases by inducing cellular proliferation and attrition events that alter the composition of the memory T-cell compartment. For instance, viral infections both introduce new lineages into the memory repertoire and deplete existing lineages through direct or bystander effects. We quantify how particular proliferation and attrition events impact the memory CD8+ T-cell repertoire using a combination of Markov processes and probability distributions. This provides insight into how the immune memory repertoire as a whole is affected by individual lineage dynamics.

8. Interpreting Labeling Data Set of CFSE and Thymidine on Division Histories of B Cells

Ha Youn Lee
University of Rochester, NY

The fluorescent dye carboxyfluorescin diacetate succinimidyl ester (CFSE) classifies proliferating cell populations into groups according to the number of divisions each cell has undergone (i.e., its division class). The pulse labeling of cells with radioactive thymidine provides a means to determine the distribution of times of entry into the first cell division. We derive in analytic form the number of cells in each division class as a function of time using the cyton approach that utilizes independent stochastic distributions for the time to divide and the time to die. We confirm that our analytic form for the number of cells in each division class is consistent with the numerical solution of a set of delay differential equations representing the generalized Smith–Martin model with cell death rates depending on the division class. Choosing the distribution of time to the first division to fit thymidine labeling data for B cells stimulated in vitro with lipopolysaccharide (LPS) and either with or without interleukin-4 (IL-4), we fit CFSE data to determine the dependence of B cell kinetic parameters on the presence of IL-4.We find when IL-4 is present, a greater proportion of cells are recruited into division with a longer average time to first division. The most profound effect of the presence of IL-4 was decreased death rates for smaller division classes, which supports a role of IL-4 in the protection of B cells from apoptosis.

9. Mathematical and computational modeling of the replication kinetics of swine-origin, avian, and seasonal influenza strains.

Hugh Mitchell*1, Drew Levin*2, Catherine Beauchemin3, Alan Perelson4, Stephanie Forrest2, and Fred Koster1

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The dynamics between host immune response and pathogen replication at the mesoscopic level require exploration by deterministic and stochastic approaches. The pathogenicity and transmissability of pandemic strains are likely determined in part by replication efficiency in human cells, but quantitative tools for phenotyping replication are underdeveloped. To better understand the innate immune response to influenza viruses, we investigated the infection kinetics of three influenza strains of varying transmissibility and pathogenicity in highly differentiated human bronchial epithelial cells in air-liquid interface cultures. A differential equation model, incorporating virion release delay and cellular antiviral response components, was used to determine basic kinetic properties of the infection process in the context of the three strains. In addition, two distinct spatially explicit agent-based computational models were implemented. One of these spatial models was built using CyCells, a flexible three-dimensional modeling tool that replicated our results in the established agent-based modeling program ma_virions. Modeling demonstrated that values of cellular R0 , the index of replication efficiency, for avian H5N1 1997 (3.0 - 4.0), seasonal H1N1 1999 (14-21) and swine-origin H1N1 2009 (48-73) influenza strains mirrors the pattern of populational R0 values for these strains, and that cellular inhibition varies markedly among the strains. Interestingly, cell life span did not appear to vary noticeably between strains. Using this synergistic experimental-computational approach, phenotyping of influenza strains in human respiratory cells can be enhanced by modeling parameters inaccessible to experimental measurement.

* H. Mitchell and D. Levin contributed equally to this work.

10. Predicted Confounding Effect of Weakly Immunogenic Long-Lived Infected Cells on Vaccination against Simian Immunodeficiency Virus

Igor Rouzine

Tufts University, MA

Although vaccination with SIVmac251 is unable to prevent chronic infection upon challenge with the same virus, a representative vaccinated macaque establishes a lower steady-state virus level (~ 30 fold on average), higher CTL frequencies (~ 10-fold), and much higher (a few orders of magnitude) helper cell frequencies, than a representative control animal.

Our previous model, selected to match several important features of cytotoxic immune response to various viruses including HIV, predicted the existence of two steady states with the described properties: Unvaccinated animals end up in the high-virus state, and vaccination, at high initial levels of memory cells, forces the system after challenge into the low-virus state. However, if we try to apply this prediction to vaccinated animals, we conclude that the level of viremia in the low-virus state is surprisingly high (e.g. as compared to animals challenged with SHIV) and strongly variable among individual animals (3-4 orders of magnitude). Our general aim is to understand why the virus load required to maintain a constant helper response in the "low-virus" state in vaccinated animals is so large and variable. There are two major possibilities: Either the dominant infected cells are weakly immunogenic, or the helper cells have very low sensitivity to antigen.

Here we investigate the first scenario. In addition to the short-lived (~ 1day) infected cells featuring in the previous model, we introduce a second infected cell type, which is longer-lived, produces less virus, and, hence, has less of an impact on the immune system. These cells are predicted to dominate the steady state infection in vaccinated animals, when highly productive cells are rapidly eliminated by fast activation of memory CTL produced by vaccination. We link this hypothetical cell type to the second, slow phase of viremia decay under ART (Perelson et al 1997) and the infected cells with low HIV RNA content observed in the lymphoid tissue (Cavert et al 1997; Zhang et al, 1999). Experiments are proposed to confirm or refute the importance of long-lived infected cells in vaccinated animals.

11. A stochastic model of and viral load and viral blips in HIV patients on ART

Jessica Conway

University of British Columbia, Canada

While on anti-retroviral treatment (ART) for HIV, an infected individual's viral load remains non-zero, though it is very low and undetectable by routine testing. However, blood tests show occasional viral blips: very short periods of detectable viral load. Viral blips have been shown to be unassociated with patient or demographic variables, and to be only marginally associated with reported episodes of nonadherence to treatment. Further, there is evidence that the virus is closely related genetically to the pre-treatment virus, suggesting that the low viral load is not due to ongoing (and error- prone) viral replication. We present a stochastic model that shows that this very low viral load can be explained principally by the activation of cells in the latent reservoir, seeded before the initiation of treatment, and that viral blips represent large deviations from the mean. The model is validated through direct numerical computation and comparison with patient data and allows us to estimate blip frequencies, magnitudes and durations. Finally we discuss the implications of our model on the emergence of drug resistant HIV in treated patients.

12. A quantitative characterization of antibody responses to Bordetella pertussis and Bordetella parapertussis

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Bodetella pertussis is a causative agent of whooping cough; an endemic disease in much of the world which causes an acute illness characterized by severe coughing that can progress to become spasmodic, and in some cases, lead to death. The immune response against these bacteria is reasonably well studied but its quantitative characterization is still lacking. Recently it has been reported that *B. parapertussis* also contributes to this disease and activates a similar immune response, making a quantitative characterization even more important. Though *B. parapertussis* and *B. pertussis* are closely related to each other, they have a repertoire of distinct virulence factors. In this manuscript we develop a simple mathematical model which was used to develop two competitive hypotheses. First is a minimalist phagocyte-centric hypothesis (PCM) that describes the minimal numbers of components sufficient to reproduce the bacterial growth curves in wild-type mice. Second, an antibody-centric hypothesis (ACM), evaluates the role of antibody responses by reproducing the growth curves in wild-type and B cell deficient mice. ACM addresses the discrepancy between the timing of B cell activation and the antibody response by parameter estimation. With the estimated parameters we could reproduce the observed antibody responses to both pathogens. We estimated two critical rate constants namely, a rate of phagocytosis of antibody-antigen complexes and a rate of cytokine induced recruitment of phagocytes. Furthermore, we provide an approximate estimation for the rate of antibody binding to the bacteria and the rate of antibody response.

13. How natural host species avoid CD4+ T cell depletion: insights into the pathogenesis of HIV

Ming Liang Chan[1], Petravic, J. [1], Ortiz, A. [2], Engram, J. [2], Paiardini, M. [2], Cromer, D. [3], Silvestri, G. [2, 4], Davenport, M. P. [1]

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Human immunodeficiency virus (HIV) infection involves the progressive decline of CD4+ T lymphocytes, resulting in severe immune deficiency. This in turn leads to opportunistic infections and cancers characteristic of AIDS, and eventually death. HIV is derived from simian immunodeficiency virus (SIV), which infects primates. It has been observed that natural hosts of SIV, such as Sooty Mangabeys, are largely asymptomatic when infected. This is sharply contrasted with non-natural hosts of SIV, such as Rhesus Macaques, and untreated HIV-infected individuals, who experience progressive depletion of CD4+ T cells in the blood and lymphoid tissues, and go on to develop AIDS. Currently, the lack of disease progression in natural hosts of SIV is still not clearly understood. A better understanding of why SIV is not pathogenic in natural hosts will therefore provide valuable insights into the pathogenesis of AIDS in HIV-infected individuals.

Experimental data show that as CD4+ T cells are depleted during infection, there is an increase in the proliferation rate of the remaining CD4+ T cells [as measured by Ki67 expression]. However, Sooty Mangabeys show only a small increase in the fraction of proliferating CD4+ T cells compared to larger increases in Rhesus Macaques and HIV-infected individuals. This suggests that disease progression is associated with the marked differences in the homeostatic proliferation of CD4+ T cells in response to CD4+ T cell depletion. In our study, we have developed a model that demonstrates the relationship between proliferation and disease outcome to help us understand why SIV is not pathogenic in Sooty Mangabeys, while in SIV-challenged Rhesus Macaques and HIV-infected individuals, infection leads to AIDS.

Modelling of this relationship suggests that a slower, but still effective, homeostatic response to CD4+ T cell depletion in non-pathogenic SIV infection paradoxically leads to preservation of higher CD4+ T cell levels during chronic infection. The results indicate that one of the key mechanisms by which natural hosts have adapted to SIV infection is by attenuating their proliferative homeostatic response to chronic CD4+ T cell depletion.

14. Mathematical models of persistent infections

B. Kochin(1), Philip Johnson(1), J. Blattman(2), R. Regoes(3) and R. Antia(1)

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We model CD8 T cell responses to persistent infections by incorporating immune exhaustion into existing models of acute infections. Our model qualitatively describes the dynamics of mice with ARM and Clone13 strains of the LCMV that cause acute and chronic infections respectively. We then validate this model by predicting the dynamics of Clone13 LCMV infections after adoptive transfer of increasing numbers of P14 cells specific for the GP33 epitope of LCMV into mice prior to infection (Blattman et al 2009 JV). In particular, the model can explain how the transfer of: (i) a few P14 cells leads to chronic infection; (ii) an intermediate number of P14 cells leads to host death; and (iii) a large number of P14 cells leads to either pathogen clearance or a chronic infection with escape variants of the virus. We then extend our model to consider antigenically varying pathogens such as malaria and HIV that cause persistent infections, with startling results that run counter to conventional wisdom concerning the importance of cross-reactive immune responses.

15. New analytical approaches for measuring SLOW dynamic processes in immune disorders

Robert Busch

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Homeostasis is a fundamental property of living systems, shared by the immune system. It is maintained by balancing the rates of production and destruction of immune system constituents to maintain a steady state, which is perturbed during immune responses. The rates of slow dynamic processes are of particular interest in autoimmune pathophysiology, where chronic immune activation results in slowly progressive damage to affected organs. Systemic dysregulation of immune homeostasis is a feature of several autoimmune diseases and may contribute to pathophysiology and pathogenesis. Target organ damage may accumulate over years and is difficult to modify by therapy; the disease course varies between patients, and long time scales are therefore required to detect hard clinical outcomes. Our work focuses on quantifying rate constants for the production and destruction of immune components and for damage to target organs of autoimmune disease. Technological advances have made these dynamic aspects of autoimmune disease increasingly accessible to direct measurement. In particular, biosynthetic labelling with heavy (deuterated) water (^2H_2O) has emerged as a versatile tool for quantifying homeostatic abnormalities on time scales ranging from hours to months. ^2H_2O can be administered orally or parenterally to humans or animals and has an excellent safety record. It equilibrates rapidly within body water and can be maintained at constant enrichment over many weeks, for extended continuous labelling experiments. ^2H from ^2H_2O enters many biosynthetic pathways, including those for protein synthesis (via nonessential amino acids) and DNA replication (via *de novo* nucleotide synthesis). Fractional replacement rates of proteins or cells can then be measured by tracking the incorporation of ^2H into appropriate analytes, derived from proteins or cells of interest, using mass spectrometry. Over the past decade, mass spectrometric techniques have evolved to improve specificity, as well as sensitivity for low amounts of label or analyte. I shall discuss how these analytical improvements are opening up new opportunities for rheumatology research. Relevant examples include probing mechanisms of systemic immune activation and CD4 lymphopaenia in primary Sjögren's syndrome, measuring fibrogenesis as a marker of end-organ damage in scleroderma, and exploring homeostatic regulation of antigen presentation in the context of MHC-linked autoimmune disease susceptibility.

16. Mathematical modelling of lymphopenia induced proliferation

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We use a mathematical modeling approach to compare the proliferative response of TCR transgenic F5 and OT-1 T cells to lymphopenia (see Hogan et al. for details on experimentations). We compared several statistical approaches based either on weighted sum of square or likelihood through simulations and on real data. We have also explored the identifiability of parameters according to the data available and the complexity of the model. Based on the available data, the single stochastic divisions_ Smith-Martin_ model was better adapted than the 'autopilot' deterministic model for OT-1 T cells, as previously shown on F5 cells only. Moreover, we compared several extension of the Smith-Martin model, allowing the rate of division to vary according to the time, the current number of cycle or the current number of cells and also including a death term. Hence, the best model (with the lower AIC) revealed no significant death (in agreement with the stability of the number of precursors) and included a transition rate to proliferative phase that decreased across time. This was true for the two types of cells: OT1 and F5. However, the parameters differed between the two types of cells: the lag time before any division was longer for F5 than OT1, the baseline rate at which T cell were triggered into cell division was lower for F5 than OT1.

We discuss some extension of the model, incorporating additional data (Ki67+) and the possibility of staying several rounds in proliferating phase before coming back to resting phase.

ANR-BBSRC RHOMEO project part 2.

17. In vivo quantification of the effect of IL-7 on proliferation, survival and production of CD4+T cells: mathematical analysis of one phase I study in HIV-1 infected patients.

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Background: IL-7 is known to increase intra and extra-thymic proliferation as well as survival of T cells. A phase I study has shown that IL-7 administration in HIV-infected patients leads to an increase of T cells *(Y. Levy et al, JCI 2009)*. However, the relative contribution of production, proliferation and survival to this increase has not been quantified.

Methods: The trial included 13 ART–treated HIV-infected patients whose CD4+ cell counts were between 100 and 400 cells/µl and plasma HIV RNA levels were less than 50 copies/ml. Patients received a total of 8 subcutaneous injections of 2 different doses of recombinant human IL-7 (rhIL-7; 3 or 10 µg/kg, dose 1 and 2, respectively) 3 times per week over a 16-day period. We used 11 repeated measurements of total CD4+ T cell count and Ki67+ positive cells among CD4+ T cells up to 48 weeks.

We used a mathematical model including two compartments: the quiescent CD4+ T cells (Q) and the proliferating CD4+ T cells (P). Q cells were produced at a rate lambda and proliferated at a rate pi. P cells reversed at a rate rho (1/rho representing the average duration of Ki67+ expression). Death rates of Q and P were µq and µp respectively. Parameters were estimated using a maximum likelihood approach taking into account individual variability of parameters through random effects. Models were compared using the Akaike criteria (AIC).

Results: Peaks of CD4+ and CD4+Ki+ cells were observed at 14 days, followed by a steadily decrease of both markers. In a first model (AIC=151), IL-7 was assumed to influence proliferation only during the period of IL-7 administration. There was a strong effect of IL-7 on proliferation rate changing from 0.0396/day to 0.112/d with dose 1 and 0.193/d with dose 2 ($p<.001$). As expected, the estimated death rate for Q was lower than for P (µq=0.032/d, µp=0.174/d). A second model that took into account an additional effect of IL-7 on the death rate of quiescent cells (µq) after 16 days provided a better fit of data (AIC=131). The death rate decrease after 16 days from 0.067/d to 0.059/d with dose 1 and 0.052/d with dose 2 ($p<.0001$). There was still a strong effect on the proliferation rate. The estimated rate of input of CD4+ cells was 9.3 cells/μl/d and was not significantly modified during IL-7 administration.

Conclusion: The quantification of the in vivo effect of IL-7 using a mathematical model showed a significant effect on cell survival in addition to peripheral proliferation. The model and estimates should be confirmed with additional data (to be available through another phase I trial). This approach should also help in predicting individual response to IL-7 as well as to design future trials using simulations.

18. Immune System Decision-Making by Detection of Pathogen Growth

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One of the central goals of immunology has been to understand the cellular and molecular mechanisms of immune regulation. Progress on the cellular front developed rapidly in the late eighties when Mosmann and Coffman identified Th1 and Th2 cells as two distinct CD4 T-cell populations with unique functions and patterns of cytokine production. For almost 20 years following the discovery of Th1 and Th2 cells, the Th1/Th2 paradigm dominated immunological thought: Th1 cells were regarded as being critical for defense against intracellular microorganisms, while Th2 cells were viewed as necessary for defense against extracellular pathogens. Proper immune regulation was then understood as resulting from the appropriate balance between these two T-cell populations, with autoimmunity and allergies emerging from an overabundance of Th1 and Th2 cells respectively.

Just as the Th1/Th2 model of immune regulation helped to further our understanding of the cellular mechanisms of immune regulation, the discovery of Toll-like receptors (TLRs) in the late nineties resulted in rapid progress towards an understanding of the molecular mechanisms of immune regulation. Immunologists now recognize a wide array of pathogen associated molecular patterns (PAMPs) capable of activating the immune system through interaction with a number of pattern recognition receptors (PRRs) expressed by cells of the immune system.

Despite the success of the Th1/Th2 paradigm and the recent focus of immunologists on PRRs, many aspects of immune regulation remain unexplained. Recently, for instance, immunologists have discovered two new T-cell populations – induced regulatory T-cells (iTreg) and Th17 cells. How iTreg and Th17 cells integrate with Th1 and Th2 cells remains an active area of research. Similarly, while PRRs have proven useful in elucidating immune defense against a wide array of different pathogens, currently established PRRs are not sufficient to explain all instances of immune activation.

Recently, I proposed a novel mechanism of immune regulation based on detection of pathogen growth (Bewick et. al, available at PLoS ONE 12/02/09). I termed this novel mechanism the Growth Detection Paradigm (GDP) and showed how it arises naturally as a result of the signaling interactions and maturation kinetics of iTreg and Th17 cells. Building off of the basic premise of the GDP model, I now extend the iTreg/Th17 system to include additional immune effector cells. With this extension, the GDP model can now explain even more detailed aspects of immune decision-making while maintaining the same robustness and sensitivity that characterized the basic GDP decision-making framework.

19. Understanding HIV Genetic Diversity - A Population Genetics Approach

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During an HIV infection, the HIV population experiences dramatic changes in both its population size and its genetic composition. The population size changes experienced by HIV are well studied empirically, with an initial acute phase of population expansion and contraction followed by a long chronic phase of stable population size. These population size dynamics have also been extensively modeled and analyzed from a theoretical perspective. On the other hand, the genetic evolution of HIV during an infection is not well understood and has received far less attention from theorists. For example, several empirical studies have shown that HIV genetic diversity increases during infection until finally reaching a high point and beginning to drop right before the onset of AIDS, however no model currently exists to explain this behavior. Modeling HIV genetic evolution requires an understanding of the complex interaction between the HIV population and the immune system. One key aspect of this interaction is the relationship between CTL attack on HIV infected cells and the genetic diversity of HIV. In this talk we explain a model that begins to explore this issue. We show that under our model CTL attack can create enormous genetic bottlenecks in the HIV population, and we show that the size of these bottlenecks depends on the reaction time of the immune system. Our model and results borrow ideas from the field of population genetics. We will explain these ideas, and more generally attempt to connect current population genetics theory to the open problems that exist in HIV modeling.

20. Immune Systems as Complex Learning Machines

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We seek feedback on a research agenda. We view immune systems as learning machines that extract information from their environments, encoding it in an internal representation that enables the machine to improve its performance (measured as host survival) over time.

The core observation arising from this thesis is that such machines can operate in at least two performance regimes. In a "stationary environment", the machine faces an essentially fixed distribution of environmental stimuli, such as an individual that faces a predominantly fixed population of pathogens in its lifetime. This regime corresponds to "classical" learning machines, which display a characteristically-shaped asymptotic learning curve. Such learning machines are well understood in the applied and theoretical learning literature, and we intend to apply those tools and techniques to understand how certain features of adaptive immunity allow effective response to a wide variety of pathogens. For example, classical learning results predict that fixed-capacity learning machines are sufficient to learn a finite complexity, stationary concept. This may explain why a fixed-length antigen-binding variable region (essentially a fixed-length pattern recognizer) in each antibody and a fixed B-cell repertoire are sufficient to recognize almost any pathogen.

However, the adaptive immune system must also perform well in a second, "non-stationary," regime, in which the environment adapts in response to the learning machine. In this regime, both pathogen and host immunity are considered learning machines, engaged in a competitive game or "arms race". For example, both immune system and pathogen "learn" to respond to each other over evolutionary time via differential survival of host organisms and pathogens. The adaptive immune system also learns to recognize an evolving population of pathogens within an individual's lifespan through somatic hypermutation. This non-stationary regime is less well studied or understood from a learning theory perspective, however fixed-capacity learning machines do not appear to model it well.

Several specific hypotheses arise from these observations:
0) When immune response and pathogen adapt at very different time scales, one is essentially stationary with respect to the other.
1) The stationary domain should produce the characteristic learning curve shape of adaptation in immune response or pathogen.
2) Organisms with long life spans, but without adaptive immunity, present a stationary learning environment to rapidly evolving pathogens. Adaptive immunity has the two-fold advantage of responding more quickly to novel pathogens and of providing a nonstationary learning environment, which is much harder for the pathogen to respond to.
3) Similarly, rapidly mutating pathogens, such as HIV, create a non-stationary learning domain for the host over the course of a single infection. This requires continual learning, which overwhelms even the adaptive immune response.
4) Over evolutionary scales, the competitive nonstationarity regime has driven the growth of complexity of both pathogen and organism.

We seek feedback on these hypotheses, including suggestions on specific organisms to examine, and data to quantify adaption/evolutionary rates and learning capacity/complexity of pathogens and immune systems.

21. A combined mathematical modelling and experimental investigation of naïve T lymphocyte homeostasis

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Regulation by homeostatic mechanisms ensures that the number and functional diversity of peripheral T cells is maintained at an approximately constant level. In the steady state, turnover of naïve mouse T cells is low. However, under conditions of lymphopenia, disruption of the homeostatic balance can induce naïve T cells to undergo cell division. This lymphopenia-induced proliferation (LIP) of naïve T cells requires signals from cytokines such as IL-7, and stimulation of the T cell receptor via interaction with self-peptide:MHC complexes. Using a mathematical model based analytical approach, we have previously shown that LIP of a monoclonal population of TCR transgenic F5 mouse T cells is best described by a stochastic single divisions model. In contrast, application of deterministic cell division models that have successfully described antigen induced proliferation, provided very poor fits to the experimental data. Under the experimental conditions used, the dividing F5 T cells retained a naïve phenotype. However, for some T cells, LIP is accompanied by a transition to a memory-like phenotype. This differentiation shares many of the cellular and molecular characteristics of antigen-driven memory cell generation, although the extent to which LIP contributes to the memory T cell pool and the specific criteria of cell division that govern such entry are unknown. Therefore, we have compared LIP of F5 T cells with that of another TCR transgenic T cell, OT-I, that acquires a memory-like phenotype during LIP. We have compared LIP by F5 and OT-I T cells in lymphopenic hosts, collecting timecourse data of cell recovery, expression of Ki67 antigen in conjunction with CFSE to provide current and historical proliferative data and expression of markers of cellular differentiation such as CD44 and CD122. This revealed profound differences in LIP F5 and OT-I T cells with respect to proliferation and differentiation. However, preliminary data suggest a stochastic single divisions model applies to both T cells, albeit with distinct model parameters (see Shuvaev et al. for details of mathematical modelling). Identification of the parameters that define the requirements for cell division versus memory transition will facilitate the development of more sophisticated models of T cell homeostasis that can successfully describe T cell behaviour in steady state replete as well as lymphopenic conditions, and predict T cell behaviour in response to specific changes in the homeostatic balance.

(ANR BBSRC RHOMEO project part I)

22. Multi-Scaled Stochastic Simulation of Cell-to-Cell Signaling

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A multi-compartment, multi-scale, agent-based simulation was developed, describing the interaction between cells in a medium. The simulation follows the stochastic processes that occur within each cell, while allowing the cells to interact with the extra-cellular medium through secretion of molecules and binding of cell-surface receptors, thus enabling cell-to-cell signaling. The extra-cellular medium is modeled by a square two-dimensional lattice, in which the cells are randomly distributed so that some lattice squares contain a single cell while other squares are vacant. Secreted molecules diffuse through the lattice using a stochastic Monte-Carlo algorithm where each molecule can move to a neighboring matrix square at each time step with a certain probability. This approach ensures that the molecules display a random walk behavior at low concentrations, while maintaining the required diffusion behavior at higher concentrations. To address the problem that the extra-cellular and intra-cellular mediums have different time scales, a modification to the Gillespie algorithm was developed. In the modified Gillespie algorithm each cell is simulated as an independent agent for a pre-defined time interval, followed by a synchronization with its local extra-cellular medium. As an example for the usability of the algorithm we simulated the response of Human dendritic cells (DCs) when infected by a virus (NDV). Infected DCs secrete interferon molecules that diffuse in the extra-cellular medium and bind to other cells. The DCs in the simulation are modeled by the number of bound interferon cell-surface receptors, and the products of the *IFNB1* and *DDX58* genes.

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